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09/288,837	04/08/1999	GENE H. MACDONALD	5470-238	7924

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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	27

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/288,837	Applicant(s) MACDONALD ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- Th MAILING DATE of this communication app ars on the cov r sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84,85,89-93 and 95-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,85,89-93 and 95-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The claims were rejected in the prior office action on the merits, mailed on November 26, 2001. The applicants' responded in paper 23, filed April 1, 2002 (Amend. E). The office sent out a notice that the communication was not fully responsive because enclosures accompanying the communication were not found. In an office letter mailed September 18, 2002, the office indicated that the enclosures had been found, and that the notice of non-responsive communication was vacated. Thus, the claims at issue in Amend. E are pending. The Amendment amended claims 84 and 95, and added claims 103 and 104. The pending claims in this case are claims 84, 85, 89-93, and 95-104.

2. The examiner and art unit to whom this case is docketed have changed. The new examiner is Zachariah Lucas of Art Unit 1648. Any future communications regarding this case should be so directed to facilitate the matching of the papers with the case.

Specification

3. **(New Objection)** The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 103 and 104 refer to Her2/neu gene products. However, the specification describes only the Her2 gene. See e.g. p. 9, lines 23-28; and p. 17, lines 33-34. The specification therefore fails to provide a proper antecedent basis for the claims to recombinant

alphavirus comprising a heterologous nucleotide sequence encoding for a Her2/neu gene product.

Claim Objections

4. **(New Objection)** Claim 95 objected to because of the following informalities: In amending the claim, although the applicant overcame the 112 rejection regarding the phrase "an immunogenically effective amount", by identifying the amount as effective "to prevent or treat cancer" the applicants both inserted the phrase "an amount effective to" and kept the phrase "immunogenically effective amount." Thus, the claim now reads "an amount effective to immunogenically effective amount to prevent or treat cancer..." It is suggested that the phrase "immunogenically effective amount" be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **(Prior Rejection)** Claims 84, 85, and 90-93 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The examiner withdraws the rejection of these claims in part, but maintains the rejections, and extends it to claims 95-104 with respect to embodiments of the claims wherein the native cancer cell antigen is derived from

the recipient of the viral composition. While the applicant has shown that embodiments of the viral vaccine that comprise antigens from other than the recipient are likely to be operative, no evidence has been presented to show that cancer cell antigens derived from the recipient of the vaccine are likely to be effective. The only data that the applicant has shown demonstrates that antigens from sources that may be homologous, but not identical to, cancer cell antigens may be operative in eliciting an antigenic response. See e.g., the Olmstead declaration (showing that rat neu genes were effective antigens is protecting/treating mice from/for tumors). As most immune systems are able to distinguish between self and foreign entities, and as the applicant has not shown that the methods disclosed would be effective where the antigens are native to the recipient of the vaccine, the applicant is not enabled for embodiments where the antigen is such an antigen.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **(Prior Rejection)** In the Action of November 26, 2001 (the prior action), claims 84, 85, 90-93, and 95-102 were rejected under 35 U.S.C. § 112, ¶ 2 for indefiniteness. There were two bases for this rejection. First, the claims were rejected because the phrase "an immunogenically effective amount" was indefinite as not stating what the amount was effective for. One reading the claim would not know the metes and bounds of the claimed invention because hey would not know what amounts were claimed. This rejection was overcome by the applicants' amendments of the claims in Amend. E. The amended claims state that the claimed compositions comprise the claimed alphavirus particles in an immunogenically effective amount to prevent or treat cancer.

The second basis for rejecting the claims under 35 U.S.C. 112 ¶ 2 is that the phrase "native cancer cell antigen" is indefinite. The phrase could mean either an antigen that is naturally occurring, or could be limited to antigens expressed by the recipient of the claimed composition. The applicant responded by discussing two possible embodiments of the claimed invention, those where the cells of the recipient are manipulated to express an artificial cancer antigen, or an embodiment wherein the cancer cells from another source are manipulated to express the antigen. The applicant then stated, "according to this embodiment, the exogenous cancer cells will typically need to share an antigen with the cancer subject's cells in order to effectively induce an immune response thereto." No further statements were made as to what exactly was meant by the phrase.

While it may be required that the exogenous cells share an antigen with the recipient's cells, this does not resolve the issue at hand. As was described in the prior action, the specification poses two definitions for the phrase. The applicants' amendment merely restates the fact without resolving the problem. While both the two antigens may be shared, this does not state whether the antigens are derived from the cells of the recipient or from cells from another donor. Therefore, the claims as written read on both alphaviruses comprising nucleotides encoding for cancer antigens native to the recipient, and on virus comprising nucleotides reading on antigens derived form other sources. Neither the applicant nor the claims states definitely whether the antigen is one that is native to the recipient's cancer cells, or one that is generically "naturally occurring" in cancer cells.

9. **(New Rejection)** Claims 103 and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. Each of these claims refers to a Her2/neu gene, however the specification discusses only a Her2 gene. Although the neu and the Her2 genes are generally considered to be the same, because the applicant has changed the way they genes are being referred to between the specification and the claims, it is unclear if the applicant intends the new phrase to refer to the same gene. The claims are therefore rejected for indefiniteness.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. **(New Rejection)** Claim 84, 85, 92, 93, 95, 96, 98, 100, and 102 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,843,723, issued to Dubensky et al. These claims read on recombinant alphavirus vectors comprising native cancer cell antigens, including embodiments wherein the virus is the Venezuelan equine encephalitis virus (VEEV).

Dubensky teaches recombinant alphavirus that are used as vectors capable of expressing heterologous sequences. Col. 1, lines 19-22. Among the alphaviruses taught for use as such a vector is VEEV. Col. 4, lines 20-26. The patent teaches that the alphavirus may be used to encode a number of proteins including "native or altered cellular components, as well as foreign protein or cellular constituents..." Because the patent describes the native proteins as "cellular components," it is clearly indicating that the proteins are native to the target cell and not the virus. See also, col. 37, lines 55-59, (the term "native antigen" is treated as referring to antigens not native to the alphavirus genome). The patent is therefore teaching that the alphaviruses may be used to encode and stimulate immunogenic responses against antigens that are both foreign and native to the target cell. The patent also indicates that non-tumorigenic antigens may be used without alteration. See, col. 27, lines 5-8 (teaching that alterations are required to make tumorigenic antigens non-tumorigenic- thereby indicting that no change need be made to non-tumorigenic antigens). The patent also teaches that the viruses may be modified such that the viral transcription of the region of the virus encoding the structural protein is not transcribed (therefore the virus is attenuated). Col. 2-3, and col. 2, lines 25-29. Therefore, the patent anticipates the claimed embodiments comprising attenuated VEEV vectors comprising cancer cell antigens that are native to the cells.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. **(New/Renewed Rejection)** Claims 84, 85, 90-93, and 95-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over either 1) Johnston et al., WO 95/32733 or 2) U.S. Patent Number 5,843,723, issued to Dubensky et al. in view of U.S. Patent 5,792,462, issued to Johnston et al. (Johnston 2), with either 1 or 2 further in view of Falo et al., U.S. Patent Number 5,951,975. These claims read on recombinant alphavirus comprising nucleic acid sequences that encode native cancer cell antigens. For the purposes of this rejection, the phrase "native cancer cell antigen" is being read as including embodiments where the antigen is one shared by the donor and the vaccine recipient, but where the antigen was not derived from the recipient of the viral vaccine.

Johnston teaches a VEEV comprising an antigenic heterologous nucleic acid. Abstract. The reference teaches that the heterologous nucleic acid may be associated with a 26S promoter (p. 7, lines 13-15), and teaches attenuating mutations to the VEEV genome that may be used to create an attenuated virus for use as the antigen vector. Among the attenuating mutations that may be used are mutations at codons at E1 amino acids 81 or 253 (p. 3, lines 19-23), mutations at codons at E2 amino acids 76, 120, or 209 (p. 5, lines 26-32), and a mutation comprising an inactivated cleavage recognition site at E3 amino acids 56-59 (p. 3, col. 21-23). However, Johnston does not teach the inclusion of a cancer antigen in the virus.

Dubensky teaches recombinant alphavirus that are used as vectors capable of expressing heterologous sequences. Col. 1, lines 19-22. Among the alphaviruses taught for use as such a vector is the Venezuelan equine encephalitis virus (VEEV). Col. 4, lines 20-26. The patent teaches that the alphavirus may be used to encode a number of proteins including "native or

altered cellular components, as well as foreign protein or cellular constituents..." Because the patent describes the native proteins as "cellular components," it is clearly indicating that the proteins are native to the target cell and not the virus. See also, col. 37, lines 55-59, (the term "native antigen" is treated as referring to antigens not native to the alphavirus genome). The patent is therefore teaching that the alphaviruses may be used to encode and stimulate immunogenic responses against antigens that are both foreign and native to the target cell. However, while Dubensky teaches that the virus may be made to express tumor antigens (cols. 23-25), it also teaches that such antigens must be altered to make them non-tumorigenic if they are so in their native form. Therefore, the patent does not teach that the virus may include native cancer call antigens. Nor does the patent teach the claimed mutations that lead to the virus attenuation.

However, the claimed attenuation of the viral vectors would have been obvious when Dubensky is seen in view of Johnston 2. Johnston 2 teaches the attenuation of viral vectors so as to prevent the viral vectors from being able to cause disease in hosts to whom they are injected. Col.1, lines 40-59, and col. 6, lines 28-35. The attenuating mutations taught by the reference include mutations at the codons at E1 amino acids 81, 253, and 272, and at the codons at E2 amino residues 76, 120, 209. Col. 6, lines 28-67. As the purpose of the attenuation taught by Dubensky would have been to reduce viral virulence, and as the same was true of the Johnston 2 attenuations, it would have been obvious to one of ordinary skill in the art to substitute the Johnston 2 substitutions with those of Dubensky. Thus, from the combination of the Johnston 2 and Dubensky patents, it would have been obvious to one in the art to make a viral vaccine vector comprising an attenuated VEEV. However, neither these references, nor the Johnston

reference above, teach the inclusion of nucleic acids encoding native cancer cell antigens in the VEEV vectors.

Falo teaches the stimulation of a subject's immune system through a two-step immunization process. Col. 3, lines 46-65. However, what the patent is teaching in a method wherein the subjects immune system is being sensitized to an antigen that is expressed on cancer cells in the subject. The method does this first by immunizing the subject with the antigens, then by administering to the subject an inoculation of cells derived from their own cancer cells, but engineered to express the antigen. Among the antigens taught by the patent is the Her2 antigen. Col. 4, line 31. While Falo does not teach the use of a viral vector to introduce the antigens, it would have been obvious to one of ordinary skill in the art to use the antigens of Falo in the viral vectors of either Johnston, or of Dubensky in view of Johnston 2. Each of the viral vectors are taught to be effective against multiple diseases, and Falo is simply identifying antigens that may be use to target cancer or tumors. In either case, one of ordinary skill in the art would have been motivated to combine the references to make a viral vaccine that is effective to treat cancer. One of ordinary skill in the art would have had a reasonable expectation of success because Falo shows that the antigens were effective in eliciting an immune response. In responses to prior actions, the applicant has argued that this rejection is invalid for two main reasons.

In Amendment file October 2, 2001, the applicant argued that the antigens taught by Falo are different from the native cancer antigens taught by the applicant on the basis of the use of the adjective "artificial" to describe the antigens used by Falo. This is not found persuasive. The applicant argues that the only sensible use of the term "artificial" is to describe an antigen that does not naturally occur on the surface of the cancer cell. The examiner does not agree,

especially when Falo explicitly states that "[e]xamples of human TRAs which may be utilized in the present invention include but are not limited to MAGE-1, MAGE-3, Melan-a, gp-100, p53, CEA, and HER2/neu." Col, 4, lines 29-31. This indicates that naturally occurring cancer antigens may be used. Therefore, a more fitting definition of the term "artificial" in Falo would be an antigen that originates from a source other than from expression of DNA native to the cell.

It is this later definition that the examiner is using to make the current rejection. The applicant has attempted to distinguish the claimed antigens from those of Falo on the basis of this "artificial' versus "naturally occurring" classification. However, the claims read on antigens that are derived from sources other than the recipient. As such, the claims read on viral vaccines wherein the antigen is a naturally occurring cancer cell antigen from a donor other than the recipient. An example is shown in the Olmstead Declaration. In this declaration, the "native cancer cell antigen" used to vaccinate mice is a rat neu gene product. In such a case, the viral vectors encode a native cancer cell antigen that has no relation at all to the murine recipients. Therefore, the applicant has failed to distinguish between the antigens of the claimed inventions, and those taught by Falo.

The applicant also argues that there is an unexpected property of the present invention over what would have resulted in the combination of the prior art references. However, in making this argument, the applicant has focused on the distinction between the Falo reference and the methods of using the claimed invention described in the present application. The applicant argues that Falo requires a two-step process while the claimed inventions may be used in a method with a single inoculation. However, the applicant has failed to consider the 103 references as a whole. While Falo teaches a two-step method, neither the Johnston nor the

Dubensky references, which disclose the use of the viral vector that the Falo antigens will be used in, require such a two-step method. See e.g., Dubensky, col. 47, lines 13-34; and Johnston, p. 2,lines 17-25. Therefore, the fact that the claimed viral vaccine may be used in a single step method, while the cellular composition of Falo requires two steps is irrelevant as the antigen of Falo would have been inserted into the viral vectors of the other references, and would therefore have been used according to the methods of Johnston and Dubensky.

Conclusion

14. The following prior art reference is made of record and is considered pertinent to applicant's disclosure for the below stated reasons.

U.S. Patent Number 5,843,723, issued to Dubensky et al. The teachings of this patent are described in part above. The patent also teaches embodiments here the cancer antigen is a neu gene product. Col. 24, line 7.This reference is however not cited in a prior art rejection of claims to naturally occurring tumorigenic proteins because it does not teach the use of unaltered tumorigenic cellular proteins to elicit immune responses against tumor cells. The patent specifies that tumorigenic proteins, which neu is, must be altered to render them non-tumorigenic. Co. 27, lines 5-7. Because the present application teaches the use of an antigen native to (and therefore unaltered) the cancer cell, the claims do not read on the altered virus taught by the Dubensky patent.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
October 7, 2002

JAMES HOUSEL 10/20/02
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